Mapping the effect of APOE ε4 genotype on intrinsic functional network centrality in patients with amnestic mild cognitive impairment

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Target audience Researchers studied on translational medicine in neuroimaging and neuropsychiatric disorders.

Purpose The independent contributions of cognitive and genetic risk factors (i.e., amnestic mild cognitive impairment [aMCI] and apolipoprotein E [APOE] ε4 allele) for Alzheimer's disease (AD) have received considerable attention, but less is known about possible interactive effects. Specifically, in this study we sought to determine whether APOE-ε4 is linked to a specific pattern of intrinsic functional disintegration of the brain in aMCI patients and how the APOE genotype specifically modulates the disease phenotype.

Methods We carried out whole-brain exploration of functional connectome using resting-state functional magnetic resonance imaging (R-fMRI) data from a substantial sample of aMCI patients (27 ε4 carriers and 39 non-carriers) and healthy subjects (45 ε4 carriers and 45 non-carriers), through analyzing voxel-wise network centrality (e.g., functional connectivity strength [FCS] and eigenvector centrality [EC]) that capture different aspects of whole-brain information flow within the connectome. Briefly, FCS is a local measure of the connectome graph indexing the number of direct connections for a given node [1]. By contrast, EC is a relative global measure that indexes the qualitative superiority of a node's connections, rather than the number of direct connections per se [2]. Accordingly, voxel-wise analysis of covariance (ANCOVA) models were used to investigate the possible diagnosis × genotype interactions on local and global information processing within the functional connectome, followed by post-hoc pairwise comparisons.

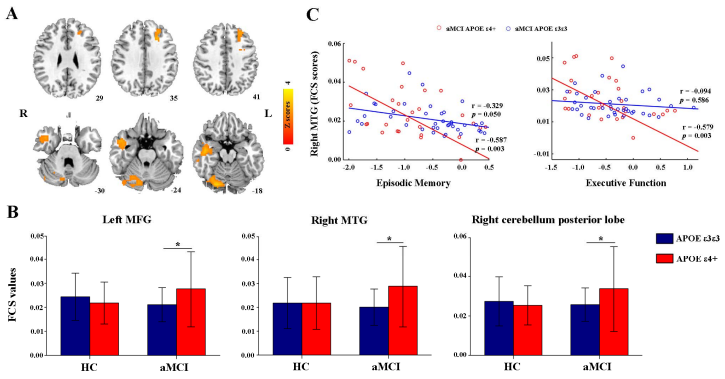

Figure 1 Diagnosis-by-genotype interactions on FCS.

Results We observed significant diagnosis × genotype interactions on FCS in the right middle temporal gyrus (MTG), left middle frontal gyrus (MFG) and cerebellum posterior lobe (**Figure 1A**). Significant diagnosis-by-genotype interactions on EC were also observed in the right MTG, bilateral orbitofrontal cortex (OFC) and retrosplenial cortex (RSC) (**Figure 2A**). Interestingly, post-hoc analyses revealed that ε4 carriers showed significantly higher FCS and EC in the right MTG than non-carriers in the aMCI group (**Figure 1B and Figure 2B**). We further observed opposite effects of the APOE genotype on network centrality in the aMCI group; aMCI ε4 carriers showed increased FCS in the left MFG and cerebellum posterior lobe, but decreased EC in the bilateral OFC and RSC than non-carriers (**Figure 1B and Figure 2B**). Note that in the post-hoc analyses, such genotype differences were absent in the healthy control group. In addition, correlative analyses revealed that regional FCS values in the right MTG negatively correlated with the episodic memory and executive function only in aMCI ε4 carriers (**Figure 1C**).

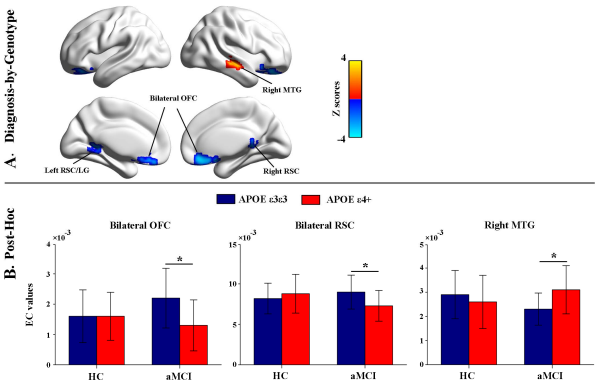

Figure 2 Diagnosis × genotype interactions on EC.

Discussion and Conclusion In this study, our main finding is that the APOE-ε4 is linked to a specific pattern of intrinsic functional disintegration of the brain in aMCI patients. Specifically, when examining APOE genotype effects in the aMCI group, FCS mainly revealed ε4-related increases in centrality within the MFG and MTG, but EC revealed ε4-related decreases in centrality within the OFC and RSC. These findings suggest the early onset functional reorganization of the brain network in aMCI patients carrying APOE ε4-allele; increased local (or direct) connectivity could be a result of counterbalancing ε4-related disconnections with hub-like regions within the brain at a global level.

References 1. Wang L, Dai Z, Peng H, et al. Overlapping and segregated resting-state functional connectivity in patients with major depressive disorder with and without childhood neglect. Hum Brain Mapp 2014; 35:1154-1166. 2. Di Martino, A., Zuo, X. N., Kelly, C. et al. Shared and distinct intrinsic functional network centrality in autism and attention-deficit/hyperactivity disorder. Biol Psychiatry 2013; 74:623-632.